DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 3/31/2011 has been entered.

Claims 1-44 have been cancelled; new claims 45-76 have been submitted, all of which have been considered on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45-59 and 63-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (Scale-up of Suspension and Anchorage-Dependent Animal Cells in Basic Cell Culture Protocols, Edited by Pollard et al. Humana Press Inc., 1997, pp.59-75; reference W on 892 of 2/12/2001).

Griffith et al disclose methods for scaling-up cultures of anchorage-dependent cells for the production of biological products, comprising inoculating cells onto a substrate, such as a roller bottle or

microcarrier beads, culturing the cells until they reach confluence, removing the culture media, rinsing the cells with PBS, adding trypsin to the cell culture to release the cells from the substrate, harvesting the released cells, diluting the harvested cells in fresh medium and passaging the cells (i.e. re-plating the cells) (See Griffiths et al, Section 3.2 "Anchorage-Dependent Culture" Pgs 65-71; especially Section 3.2.1.1.1 "[Roller Culture] Procedure" (at Pg. 67), Section 3.2.1.2.1 "[Glass Bead Immobilized Beds] Procedure" (at Pgs. 67-71) and Section 3.2.1.3.2 "[Microcarrier Culture] Procedure" (at Pg. 70-71)). The initial cell culture of Griffith et al reads on what Applicants are calling the 'preproduction batch', the passaged cells (re-seeded cells) read on what Applicants are calling the 'production batch', as the biological product will ultimately be produced and recovered from these cells.

Griffith et al differ from the instant invention in that, while they disclose harvesting and passaging the cells of their 'preproduction batch', they do not explicitly state the harvested cells are split into at least two portions, wherein a first portion of the cells are replated as a seed for a subsequent 'preproduction batch', and a second portion of the cells are transferred and used as a 'production batch' specifically for the production of biological products, which Applicants are calling a 'repeated discontinuous process'.

However, it is maintained that replating a portion of the cells as a seed for subsequent 'preproduction batches', and transferring a second (larger) portion of cells for use as a 'production batch' for production of biological products produced by the cells (i.e. performing a repeated discontinuous process), would have been routinely performed by one of ordinary skill in the art. The person of ordinary skill in the art, being a cell biologist having experience in maintaining cell cultures, will understand that, in standard cell culture procedure, the cell culture is harvested, and only a portion thereof is replated into each new culture vessel, in this manner, the culture is split. Splitting is necessary to prevent senescence of the cells: once cells reach confluence, they generally stop, if the culture becomes overcrowded, the

cells will die due to lack of space and nutrients; thus the culture is continually 'thinned' out in order to permit for continuation of the cell culture.

Therefore, when carrying out the protocol of Griffith et al, it would have been *prima facie* obvious to one having ordinary skill in the art to split the recovered cell culture into at least two portions, and passage (i.e. replate) the majority of the culture into a subsequent cell culture vessel for production of the biological product, and passage (i.e. replate) the smaller portion of the culture into a subsequent cell culture vessel which can be maintained as a future source of cells. One would have been motivated to split the culture as such in order to save money (by not needing to purchase a subsequent cell culture seed), and increase the amount of biological product which can ultimately be produced (as the initial culture is not exhausted after the first round of biological product production, but a small portion can be retained, passaged and expanded, so as to provide a cell source for future 'production batches'). One would have had a reasonable expectation of successfully carrying out this 'repeated discontinuous process' because the steps of splitting and passaging cell cultures, as well as steps for obtaining biological products from a 'production culture' were well known in the art (see, e.g. Griffith et al).

Griffith et al thus renders obvious a method comprising:

Inoculating the cells onto the substrate. Because the cells necessarily come from a previous cell source, the previous cell source reads on a 'working seed stock,' the working seed stock is considered to have a passage number of 0. By inoculating the cells onto the substrate the cells are passaged a first time, the cells, once present on the substrate, read on what Applicants' call a first 'preproduction batch,' the first pre-production batch has a passage number of 1 (as they have been passaged 1 time- from the working seed stock to the first culture vessel) (thereby meeting the limitations of claims 45 step (a), 50, 51, 64 step (a), 66 & 67). The substrate may be a roller bottle (solid support) or microcarrier beads (particulate matter) (thereby meeting the limitations of claims 54-56 & 68-72).

Culturing the 'preproduction batch' until it reaches confluence, at which point the culture media is removed, the cells are rinsed with PBS, trypsin (a proteolytic enzyme) is added in order to cause the cells to release from the substrate, and the cells are harvested (meeting the limitations of claims 52, 57-59, & 73-75).

Dividing the harvested cell culture into at least two portions and re-plating each portion into a subsequent cell culture vessel having an appropriate substrate (meeting the limitation of claim 45 step (b)). Each re-plated portion further cultured to expand the cell number (meeting the limitation of claim 46). The first portion is subsequently used for production of the biological product; as such the first portion is considered to read on 'a [first] production batch' (meeting the limitation of claim 45 step (c), 49 step (i), 64 step (b), and 65 step (a)). The second portion is subsequently used as a source of future production batches, and as such, the second portion is considered to read on 'a [first] subsequent preproduction batch' (meeting the limitation of claims 45 step (d), 49 step (ii), & 65 step (b)). Both the first production batch and the first subsequent preproduction batch have a passage number of 2.

When the 'first subsequent preproduction batch' reaches confluence, the method is then repeated- the culture media is removed, trypsin is added in order to cause the cells to release from the substrate, and the cells are harvested, again the cells are divided into at least two portions, each portion is re-plated into a subsequent cell culture vessel having an appropriate substrate. Again, the first portion is subsequently used for production of the biological product; as such the first portion is considered to read on 'a [second] production batch' (meeting the limitation of claim 45 step (e)). The second portion is subsequently used as 'a [second] subsequent preproduction batch' (meeting the limitation of claim 47). Each of the second production batch and the second subsequent preproduction batch have a passage number of 3; thus the second subsequent preproduction batch has a different passage number than the first production batch (meeting the limitation in claims 45 & 64 that "the cells of the at least one production batch in c) have a different passage number than the cells of the at least one subsequent production batch in e)').

With regards to the limitation in claims 45 & 64 that 'the passage number of each production batch be between master cell bank and extended cell bank' it is submitted that this range merely defines the time period (by passage number) during which cells are able to successfully produce a desired biological product; thus as long as cells are capable of producing the desired biological product, they are considered 'between MCB and ECB', one having ordinary skill in the art would readily recognize when the cells have reached a point of senescence at which the cell culture can no longer be employed. This is considered to meet the limitation of claims 63 & 76- in that the ECB would have been routinely 'fully characterized' by the person having ordinary skill in the art to determine when the cell line has exhausted its utility.

Furthermore, though Griffith et al is non-specific with regards to the type of anchorage-dependent cell as well as the biological product being produced, it is submitted that the teachings of Griffith et al are intended to be general, and thus are applicable to any well-known anchorage-dependent cell line which is capable of producing a desired biological product. MDCK cells (anchorage-dependent cells) are notoriously old and well known in the art for their use in culture to grow viruses (dating back to at least the 70s); therefore it would have been obvious at the time the invention was made that the protocols of Griffith et al were applicable to scaling-up cultures of MDCK cells for the production of viruses. Initially, though with regards to the production of viruses as the specific biological product, it is noted that the methods of Griffith et al and Pollard et al are applicable to all anchorage-dependent cell types. Furthermore, anchorage-dependent cells that are routinely cultured to product viruses are also known in the art. For example, MDCK cells are notoriously old and well known in the art for their use in culture to grow viruses (dating back to at least the 70s). Therefore it would have been obvious at the time the invention was made to split and passage MDCK cells, per the repeated discontinuous culture process discussed above for the production of viruses, thereby meeting the limitations of claims 45-58 & 64-74.

Finally, the modified method of Griffith et al still differs from the method of instant claim 48 in that there are no teaching as to the specific proportion of the cell culture to be transferred in each step; however the difference between the proportions of the total cell culture allotted for production of biological product and for use as a subsequent preproduction batch would have been routinely optimized by one having ordinary skill in the art. The proportion of cell culture which is taken out for the production batch is a result effective variable, as the amount used for the production culture directly effects the amount of product which will be produced each round. It has been held "[W]here the general conditions of a claim are disclosed by the prior art it is not inventive to discover the optimum or workable ranges by routine experimentation" See *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus the limitation of claim 42, requiring transfer of 80 to 90% of the preproduction batch for use in preparation of at least one production batch, and retaining the remaining 10 to 20% for use as a seed for production of a subsequent preproduction batch, would have been *prima facie* obvious to one having ordinary skill in the art, absent evidence to the contrary (claim 48).

Therefore, the instantly claimed method is not considered to be patentable, as it was obvious to one of ordinary skill at the time the invention was made. One would have known how to culture anchorage-dependent cells to produce a biological product, as illustrated by Griffith et al and it would be well within the purview of the skilled artisan, and generally common sense, to maintain a portion of the cell culture during each split, to replenish the original culture and use to repeat the process, thereby prolonging the culture life and increasing the amount of culture which can be used to produce the desired product.

It is further pointed out that this rationale relies on common sense and the knowledge generally available to the skilled artisan must be taken into account; such may be taken into consideration as rationale for rendering an invention patentable per the Supreme Court decision of KSR International Co vs. Teleflex Inc. Specifically, the Supreme Court held that “Variations of particular work available in one

field of endeavor may be prompted by design incentives and other market forces, either in same field or different one, and if person of ordinary skill in art can implement predictable variation, 35 U.S.C. §103 likely bars its patentability; similarly, if particular technique has been used to improve one device, and person of ordinary skill would recognize that it would improve similar devices in same way, then using that technique is obvious unless its actual application is beyond person's skill, and court resolving obviousness issue therefore must ask whether improvement is more than predictable use of prior art elements according to their established functions." See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) at 1386.

Claims 45-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiktor et al (US Patent 4,664,912; reference #2 on IDS of 6/23/2000), in view of Griffith et al (In Basic Cell Culture Protocols, 1997; reference W on 892 of 2/12/2001), and further in view of Shimizu et al (Biotechnology & Bioengineering, 1985; reference #4 on IDS of 2/22/08).

Wiktor et al disclose a method for large scale production of rabies virus in VERO cells, for use in production of a rabies vaccine. Specifically Wiktor et al discloses obtaining VERO cell line ATCC-CCL 81, the cells are provided frozen in liquid nitrogen at the 124th passage; the cells are subsequently cultured and divided to yield working seed stocks (at the 136th or 137th passages); cells of one working seed stock are seeded into a first bioreactor (See Wiktor et al, col. 4, ln 38-60). In the bioreactor the VERO cells are cultured on dextran microcarrier beads at 37°C (See Wiktor et al, col. 5, ln 14-38). At the end of the growth period the VERO cells are enzymatically released from the microcarriers by 0.025% trypsin in sodium citrate; and the VERO cells are then re-seeded on microcarrier beads in a second, larger bioreactor under the same conditions; the process is repeated in progressively larger bioreactors until a desired volume, i.e. 1000 L, is reached (See Wiktor et al, col. 5, ln 38-52). Once the desired volume is

reached, the cell culture is inoculated with a viral seed, grown to full volume, and virus is eventually produced and harvested (See Wiktor et al, col. 6, ln 10-62).

Wiktor et al differs from the method of the instant claims in that (1) they are directed to production of a virus from VERO cells, whereas the instant claims are limited to production of a virus from MDCK cells, and (2) they do not disclose subjecting the 'preproduction batch' to a repeated discontinuous process, whereby only a portion of the cells from the preproduction batch are used in the preparation of the production batch, and the remaining portion of the preproduction batch is used as a seed for the preparation of at least one subsequent preproduction batch.

With regards to (1) the type of cells: it is submitted that both VERO cells and MDCK cells were notoriously well known at the time the invention was made, are both anchorage-dependent animal cells, and were both well recognized as suitable cell types for the production of viruses. Therefore, though Wiktor et al is directed to culture of VERO cells, the method of Wiktor et al is considered to be equally applicable to MDCK cells, at least in terms of the mechanics and general protocol. Specific modifications so as to address different nutritional needs of the individual cell lines would have been routinely addressed by artisans having ordinary skill in the field of cell culture. For purposes of this rejection, the teachings of Wiktor et al regarding culture of the cells on microcarrier beads, scaling up of the cell culture volume, transferring between bioreactors, and eventual inoculation with virus in order to produce the desired viral product from the cells, is equally applicable to MDCK cells as it is to VERO cells.

With regards to (2) the repeated discontinuous process: at the time the invention was made repeated batch cultivation procedures using multiple bioreactors were well known in the art and were recognized as having the potential to increase overall productivity of a biological product from a cell culture by minimizing overall lag time (i.e. time when no culture is producing biological product). Repeated batch cultivation procedures are considered to be the same as what Applicants are calling a

'repeated discontinuous process.' For example, Shimizu et al disclose repeated batch cultivation procedures using multiple bioreactors (fermentors). In the procedure utilizing two bioreactors: cells, intended for production of a biological product, are seeded into a first bioreactor and cultured, when the cells reach a desired concentration a fraction of the first batch culture is withdrawn and transferred to a second bioreactor (i.e. is transferred as a seed for the preparation of a second batch culture). Fresh medium is added to both the first and second bioreactor. The cell culture remaining in the first bioreactor is used for the preparation of at least one biological product, after harvest of the biological product, the bioreactor is emptied. Meanwhile, the cell culture previously transferred to the second bioreactor as a seed for the preparation of a second batch culture, is cultured to yield a second culture batch. The process may then be repeated: when the cells in the second batch culture reach a desired concentration a fraction of the second batch culture is withdrawn and transferred back to the first bioreactor (i.e. transferred as a subsequent seed for the preparation of a third batch culture), and so on (See Shimizu et al, Pg. 745-747 "Repeated Batch Cultivation Using Two Fermentors" & especially Fig. 5 on Pg. 746).

The crux of the Shimizu method is that once a cell culture batch has reached a desired volume a fraction is withdrawn and used as a seed to start a subsequent cell culture batch, the remaining portion is exploited for production of the biological product. By repeatedly starting a new batch culture at the same time fermentation is initiated in the original batch culture, the lag phase of the new batch culture overlaps with the production phase of the original batch culture, thereby reducing the wait time (i.e. unproductive time) between production phases of subsequent batch cultures. In this manner the repeated batch cultivation procedures using more than one fermentor improves the overall efficiency (in terms of production of the biological product) of the system compared to a single fermentor system by reducing the wait time when no product is being produced [by any batch culture] (See Shimizu et al, Pg 754, "Discussion and Conclusions").

The method of Wiktor et al utilizes multiple bioreactors, and thus has the potential to operate on a repeated batch cultivation schedule as taught by Shimizu et al. Therefore, it is submitted that one skilled in the art would have been motivated to modify the method of Wiktor et al to function on a repeated batch cultivation schedule, using two or more fermentors, in order to eliminate the long period during which scale-up is effected. In the method of Wiktor et al, the culture is not inoculated with the viral seed until the full scale-up volume (i.e. 1000 L) is reached; thus, up until that point, no virus product has been recovered, thus the entire scale-up procedure is non-productive wait time. Furthermore, after inoculation and virus production and harvest, the method must be started over again, beginning from a new working seed stock phial, and the long period of non-productive wait time is repeated. By modifying the method of Wiktor et al to operate on a repeated batch cultivation schedule (as taught by Shimizu et al), productivity rates would be enhanced because multiple batch cultures are continually being scaled-up, thus new batches will regularly be available for inoculation with virus and viral production.

One would have had a reasonable expectation of successfully modifying the method of Wiktor et al to operate on a repeated batch cultivation schedule because the modification involves the same culture conditions, techniques, and bioreactors as used in the original method of Wiktor et al. The difference in re-seeding of the cultures is clearly taught by Shimizu et al, and is well within the purview of one having ordinary skill in the art.

In employing the repeated batch cultivation schedule of Shimizu et al in the method of Wiktor et al, the method of Wiktor et al would comprise:

Seeding cells of a working seed stock into a first bioreactor containing dextran microcarrier beads and culturing the cells at 37°C until a desired concentration is reached (producing a first batch culture). The cells of the first batch culture are considered to read on a first preproduction batch as claimed. Please note the cells of the first batch culture (first preproduction batch) were derived from the working seed

stock; the working seed stock had been passaged from the 124th passage to the 136th/137th passage, and thus the first preproduction batch was prepared from a working seed stock by at least one passage step. The cells of the first batch culture (first preproduction batch) have a passage number of 136/137- for simplicity & clarity in writing this rejection the cells will be considered to have a passage number of 137 (thereby meeting the limitations of claims 45 step (a), 50, 51, 53-56, 64 step (a), 66, 67 & 69-72).

Upon reaching confluence, enzymatically releasing the cells of the first batch culture (first preproduction batch) from the microcarriers by 0.025% trypsin in sodium (meeting the limitations of claims 52, 57, 58, 68, 73 & 74).

Re-seeding a first portion of the cells of the first preproduction batch onto microcarrier beads in a second, larger bioreactor. This first fraction of cells of the first preproduction batch will eventually be employed for the production of at least one virus, and thus is considered to read on the first production batch (thereby meeting the limitation of claims 45 steps (b) (noting the culture was necessarily divided to obtain two different fractions), 49 step (i), 65 step (a)). At the point of passage to the second bioreactor the first production batch has a passage number of 138.

Re-seeding a second fraction of the cells of the first preproduction batch cells onto microcarrier beads in the first bioreactor. This second fraction of cells of the first preproduction batch then becomes the seed for a second preproduction batch (thereby meeting the limitation of claims 45 step (d), 49 step (ii), 65 step (b)). The cells of this 'second preproduction batch' have a passage number of 138.

Fresh medium is added to both the first and second bioreactor and both cell culture batches are cultured at 37°C until the desired concentrations are reached. When the cells in the second bioreactor (i.e. the first production batch) reach appropriate concentration, they may be subsequently passaged to progressively larger bioreactors, as taught by Wiktor et al, until the batch eventually reaches a size appropriate for inoculation with a viral seed, and will be used for production of viruses (thereby meeting the limitation of claims 45 step (c), 49 step (i), 65 step (b), and 65 step (a)).

When the cells of the first production batch in the second bioreactor are recovered and passaged to progressively larger bioreactors, the process begins again: the cells are harvested from the first bioreactor (i.e. the second preproduction batch), divided, a first fraction re-seeded into the second bioreactor as a second production batch, and a second fraction re-seeded into the first bioreactor as a seed for a third preproduction batch (thereby meeting the limitations of claims 45 step (e), 47, 64 step (a) (noting all production batches technically originated from the original preproduction batch), & 65 step (a)) The second production batch and the third preproduction batch each have a passage number of 139 (meeting the limitation of claims 45 and 64 that "the cells of the at least one production batch in c) have a different passage number than the cells of the at least one subsequent production batch in e)").

With regards to the limitation in claims 45 & 64 that 'the passage number of each production batch be between master cell bank and extended cell bank' it is submitted that this range merely defines the time period (by passage number) during which cells are able to successfully produce a desired biological product; thus as long as cells are capable of producing the desired biological product, they are considered 'between MCB and ECB', one having ordinary skill in the art would readily recognize when the cells have reached a point of senescence at which the cell culture can no longer be employed. This is considered to meet the limitation of claims 63 & 76- in that the ECB would have been routinely 'fully characterized' by the person having ordinary skill in the art to determine when the cell line has exhausted its utility.

The modified method of Wiktor et al still differs from the method of instant claims 59 & 75 in that Wiktor et al does not teach treating the cells on the microcarriers with PBS and/or EDTA prior to exposure to trypsin, however, it is submitted that washing cells with PBS to remove serum-containing culture residue (as serum inactivates trypsin) was a routine step which would be recognized by one having ordinary skill in the art. Griffith et al is cited in support. Griffith et al provide a more detailed protocol on passaging anchorage dependent cells, and specifically instruct to perform a rinse with PBS prior to

addition of trypsin (See Griffith et al, Pg. 67, "3.2.1.1. Roller Culture", step 6) (thereby meeting the limitations of claims 59 & 75).

The modified method of Wiktor et al still differs from the method of instant claim 48 in that there are no teachings in Shimizu et al as to the specific proportion of the cell culture to be transferred in each step; however the difference between the proportions of the total cell culture allotted for production of biological product and for use as a seed stock would have been routinely optimized by one having ordinary skill in the art. The proportion of cell culture which is taken out as the seed is a result effective variable, as the amount withdrawn as a seed for the subsequent culture directly effects the amount of product which can be yielded by the retained production batch (the greater the proportion removed as the seed culture, the less amount of culture retained for product production (i.e. less product produced by that production batch)), and also directly effects the duration of the preparation of the next preproduction batch (the greater the proportion removed as the seed culture, the less time that will be required to grow the seed culture to the preproduction batch desired volume). It has been held "[W]here the general conditions of a claim are disclosed by the prior art it is not inventive to discover the optimum or workable ranges by routine experimentation" See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus the limitation of claim 42, requiring transfer of 80 to 90% of the preproduction batch for use in preparation of at least one production batch, and retaining the remaining 10 to 20% for use as a seed for production of a subsequent preproduction batch, would have been prima facie obvious to one having ordinary skill in the art, absent evidence to the contrary (claim 48).

The modified method of Wiktor et al still differs from the method of instant claim 60 in that Wiktor et al does not exemplify "parking" the cells after a desired cell volume of the preproduction batch has been reached. However, it is submitted that Wiktor et al does teach that the cell cultures may be

lowered from the optimal culture temperature of 35-38°C to a temperature of between 25° and 33oC in order to permit survival of the cells in a slowed-down growth phase (See Wiktor et al, col. 3, ln 41-44). The step of lowering the temperature of the culture (at any point in the method, including during culture in any one of the scale-up bioreactors) is considered to read on parking the preproduction batch of cells (as the cell cultures in each of the bioreactors except for the final bioreactor are considered to be preproduction batches) at a certain passage by exposing the cells to an ambient temperature within the range of 25° to 33°C. One having ordinary skill in the art would have been motivated to park the cultured cells by lowering the culture temperature in order to slow down the growth phase of the cells in the parked culture. While, overall, the method of Wiktor et al should comprise growing the cells as quickly as possible to maximize production of virus, at times there may be problems in the production line which would result in a back-up in upstream bioreactors, for example if one of the larger bioreactors breaks, or even if a worker is unable to cultivate or harvest the viral load in the ultimate production batch due to a schedule conflict, etc. In such cases the cell culture batches upstream of the problem would need to be parked (i.e. slow down the growth phase, while retaining viability of the cell culture) while the downstream problem is addressed. Therefore, one would be motivated to park the cells in any of the preproduction batches by the method suggested by Wiktor et al: lowering the culture temperature to between 25° and 33° C. One would have had a reasonable expectation of successfully parking the cell cultures based on the explicit teachings of Wiktor et al (claim 60). Furthermore, to restore normal growth rates after the problem is addressed, it is submitted that it would have been within the purview of one having ordinary skill in the art to simply raise the culture temperature back to the standard 35° to 38° C and passaging the cells as normal (which includes changing the culture medium) (claim 61).

Alternatively, if the problem in the production line is severe enough that it cannot be corrected in a reasonable amount of time, or if the production line was to be temporarily suspended, it would have been prima facie obvious to one having ordinary skill in the art to cryopreserve each of the cell culture

batches (within all bioreactors) and then store the culture batches until production is resumed. Wiktor et al disclose means for cryopreserving cultures of cells involving sealing the cell cultures and deep freezing the cultures in liquid nitrogen (See Wiktor et al, col. 4, ln 45-62). Liquid nitrogen stores items at -186°C (its boiling point); therefore storage in liquid nitrogen reads on the step of storing the cell culture batches at a temperature of less than -80°C, in bulk. The cell cultures would be defrosted when the production line is up and running again to restore productivity (claim 62). One would have been motivated to store the cell culture batches in each of the bioreactors in liquid nitrogen during a prolonged pause period in production so as to not waste the cells; clearly, if the cells can be stored and recovered, it would be financially desirable to store the cells as opposed to starting the scale up procedures anew. One would have had a reasonable expectation of successfully storing the cells and subsequently thawing them prior to future use because Wiktor et al report cell cultures can be expanded, subsequently frozen, and then subsequently thawed and used for production (as in their working seed stocks, derived from the master cell stock).

Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226

(Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 45-76 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 26-30, 32-34, 25-39 and 42-45 of copending Application No. 11/654,556. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims recite each of the limitations of the instant claims, though not necessarily in a single claim, the fact that each of the limitations are taught within the same application renders the instant method *prima facie* obvious..

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 10:00-7:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sue Liu can be reached on 571-272-5539. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1653